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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,482	04/06/2005	Katsuaki Miyaji	268038US0PCT	5300

22850 7590 08/05/2009

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EXAMINER	
LOEWE, SUN JAE Y	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
08/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/530,482	MIYAJI ET AL.	
	Examiner	Art Unit	
	SUN JAE Y. LOEWE	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-48,51-65 and 68-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-48,51-65 and 68-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 38-48, 51-65 and 68-74 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 7, 2009 has been entered.

Response to Amendment

3. The amendments to the claims filed on April 7, 2009 have been fully considered. The 35 USC 112 1st paragraph rejection has been obviated and is thus hereby withdrawn.

4. The search and examination was extended to include the full scope of claimed compounds. New grounds of rejection under 35 USC 112 1st paragraph and 35 USC 102 are set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 38 (and dependent claims 55, 72, 73 and 74), 39 (and dependent claims 40-42 and 56-59), 43 (and dependent claims 44-48 and 60-65), 51 (and dependent claims 52-54) and 68-71 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making "a pharmaceutically acceptable salt, prodrug or tautomer" of the claimed compounds, does not reasonably provide enablement for making "solvates." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue". The factors are applied below to the instant claims.

The breadth of the claims
Solvates (including polymorphic forms) of the claimed compounds.

The nature of the invention & the state of the prior art/level of ordinary skill/level of predictability
The state of the art for preparing polymorphic forms of any given compound is unpredictable (eg. see Chawla et al., p. 9, 1st and 2nd paragraphs):

- The number or existence of solid forms cannot be predicted.
- The more diligently any system is studied the larger the number of polymorphs *discovered*
- It is not commonly known in the art, or predictable, how different solid forms are made (Newman et al., p. 898, 2nd column, last paragraph).

The following is noted (MPEP 2164.03):

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).<
>
> .....

> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

Further, the claims insofar as they embrace solvates are not enabled. The numerous examples presented all failed to produce a solvate. The evidence of the specification is thus clear: these compounds do not possess the property of forming solvates; there is no evidence that such compounds even exist.

The state of the prior art is that an isomer is any compound having the same composition. For example, constitutional isomers fall within the scope of the claims. Constitutional isomers can contain different functional groups in varying positions. Constitutional isomers need only have the same composition of atoms as compounds of Formula Ia or Ib.

The amount of direction provided by the inventor/existence of working examples
In the instant case, there are no working examples that support of the claimed inventions of solvate, hydrate, isomer.

The quantity of experimentation needed to make or use the invention

MPEP 2164.01(a) states:

> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
>
> (A) The breadth of the claims;
>
> (B) The nature of the invention;
>
> (C) The state of the prior art;
>
> (D) The level of one of ordinary skill;
>
> (E) The level of predictability in the art;
>
> (F) The amount of direction provided by the inventor;
>
> (G) The existence of working examples; and
>
> (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Based on the evidence regarding each of the above factors (see discussion above), the specification, at the time the application was filed, would not have taught one of ordinary skill in the art how to practice the claimed invention without undue experimentation.

The instant claims *prima facie* lack enablement across the full scope claimed.

6. Claims 55-65 and 68-73 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737,

8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue". The factors are applied below to the instant claims.

The breadth of the claims
The claim is drawn to thrombopoietin receptor activator, which has the intended use of preventive, therapeutic or improving agent for diseases against which activation of the thrombopoietin receptor is effective. Diseases encompassed by the claims thus include, for example, thrombocytopenia.

The nature of the invention
It is known in the art that agonism and activation of the thrombopoietin receptor promotes increase in platelets (eg. Jelic et al).

The state of the prior art/level of ordinary skill/level of predictability
Thrombocytopenia:

- The method of treating thrombocytopenia, the condition where the amount of platelets is lowered (http://www.tirgan.com/ thrpenia.htm, page 1), depends on the cause/etiology of the disease (see for example, http://www.tirgan.com/ thrpenia.htm, page 8; Jelic et al. abstract).
- Secondary thrombocytopenia is platelet lowering due to infections. For this etiology the underlying condition must be treated in order to achieve treatment of the thrombocytopenia. One example of such condition is that resulting from HIV infection (Sundell et al., abstract). The art recognized treatment of HIV currently involves protease inhibitors and one chemokine inhibitor in phaseII/III clinical development (Simon et al., p. 494 Table 2 and p. 495 Table 3). Therefore, a correlation does not currently exist between activating thrombopoietin and treating thrombocytopenia resulting from HIV infection. It follows that correlation between activating thromobopoietin and preventing thrombocytopenia resulting from HIV infection also does not exist.
- Platelet transfusions remain the only secure means to acutely increase the platelet count in patients with imminent or actual bleeding due to thrombocytopenia caused by chemotherapy (Jelic et al., abstract; Michel, abstract). Thus, a correlation between thrombopoietin activation and prevention/improvement of thrombocytopenia resulting from chemotherapy does not currently exist.
- Thrombocytopenia can result from adverse reaction to drugs. Thus, prevention/improvement based on this etiology would require stopping the medication (http://www.tirgan.com/ thrpenia.htm, page 9-10).
- Similarly, correlation between activating thrombopoietin and preventing/improving other conditions encompassed by the instant claims, not specifically described here, do not currently exist.

The amount of direction provided by the inventor/existence of working examples
No direction/working examples, in addition to the disclosure of the thrombopoietin activating species, is provided in the specification.

The quantity of experimentation needed to make or use the invention
In the absence of working examples/direction, enablement rests on the existence of an art recognized predictable correlation between the disclosed activity and claimed intended use. Evidence suggests that this requirement is not met for the instant case. Consequently, one of ordinary skill is not enabled by the instant disclosure to practice the claimed invention. The amount of experimentation is undue.

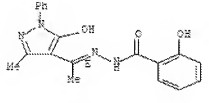
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 38-40, 51, 52, 55-57, 68, 69 and 72-74 rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al. The reference teaches the compound shown below, which is a tautomer of a claimed species (eg. B=D=methyl; A=phenyl; E=OH substituted phenyl).



The reference antedates the instant PCT filing date of October 9, 2003 (see 599166-81-1). Applicant may overcome this ground of rejection by providing a translation of the foreign documents which show support under 35 USC 112 for the claimed genus.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUN JAE Y. LOEWE whose telephone number is (571)272-9074. The examiner can normally be reached on M-F 7:30-5:00 Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sun Jae Y. Loewe/
8-2-2009